INTRODUCTION

Attendtion deficient hyperactivity disorder, a common psychiatric disorder in childhood that is characterized by pervasive and developmentally inappropriate inattention, excessive motor activity, impulsivity, and distractibility ***(Faraone, 1998)***. Due to its high prevalence worldwide (approximately 3–9 %) and severely vicious impact on the quality of life, it is necessary to understand the pathogenesis of ADHD ***(Polanczyk et al., 2007)***.

Convergent data from neuroimaging, genetics, neuropsychological, and neurochemical studies in ADHD patients have evidenced functional and structural alterations in development in several areas of the brain, Molecules implicated in neuroplasticity changes in these areas may potentially contribute to the pathogenic mechanisms ***(Cortese, 2012).***

Brain-derived neurotrophic factor (BDNF) is a neurotrophin widely expressed in the brain that plays a key role in the regulation of neurogenesis and in the differentiation of neural pathways including dopaminergic pathways during neurodevelopment as well as in the modulation of synaptic plasticity and dendritic growth in the adult brain ***(Matthew et al., 2008)***.

Endogenous BDNF may be critical for normal development and function of central serotonergic neurons, and

hence, impulse regulation ***(Lyons et al., 1999)***. BDNF is known to act as a growth and survival factor for dopamine ***(Hyman et al., 1991)*** and serotonin neurons during brain development ***(Siuciak et al., 1995)***. BDNF is also thought to prevent neuronal death.

BDNF, the most abundant neurotrophin in the brain exerts its effects by binding to the tropomyosin-related kinase B (TrkB) receptor ***(Mamounas, 1995)***. It enhances the growth and maintenance of several neuronal systems, serves as a neurotransmitter modulator, and participates in mechanisms of neuronal plasticity, such as long- term potentiation and learning ***(Theonen, 1995).***

Some reports and several lines of evidence suggest that BDNF plays a role in the pathophysiology of ADHD ***(Shim et al., 2008),*** some of these are;

First, earlier studies demonstrated that BDNF plays a key role in the survival and differentiation of midbrain dopaminergic neurons in vivo ***(Hyman et al., 1991)*** and in vitro ***(Spina et al., 1992).*** Since dysfunction in the midbrain system is crucial in ADHD pathogenesis ***(Solanto, 2002)***, a decreased midbrain BDNF activity may cause midbrain dopaminergic dysfunction, and therefore, resulting in ADHD.

Second, psychostimulants such as methylphenidate are the agents commonly used in the treatment of ADHD. The

classical action mechanism of psychostimulants involves enhancement of the release of dopamine and norepinephrine in the midbrain. BDNF has been shown to modulate the release of dopamine through activation of TrkB (tropomyosin-related kinase B) receptors ***(Blochl, 1996)***, and has also been implicated in the release of dopamine as well as in dopamine-related behaviors induced by psychostimulant, methamphetamine ***(Narita et al., 2003).***

Furthermore, psychostimulants and antidepressants are the agents commonly used for the treatment of ADHD, and both have been found to elevate central BDNF ***(Meredith, 2002)***, from the above findings, it is highly likely that elevation of central BDNF activity is important in the treatment of ADHD. This hypothesis may provide a new direction for the treatment and understanding the pathogenesis of ADHD ***(Shih-Jen, 2003)***.

Moreover, it has been demonstrated that the BDNF gene may play a role in cognitive impairment in ADHD patients ***(Cho et al., 2011)***.

A number of reports suggest a relationship between BDNF and the functioning of certain brain areas involved in attention and cognition. The highest levels of CNS BDNF are found in the hippocampus, frontal cortex, and amygdale ***(Radka et al., 1996)***. Both endogenous BDNF and intra-hippocampal BDNF infusion induce hippocampal long-term

potentiation, which is critical to the physiology of long-term memory formation ***(Messaoudi et al., 1998)***. BDNF plays an important role in the working memory of the prefrontal cortex ***(Galloway et al., 2008).***

In this study, we investigated the differences in plasma BDNF levels between children newly diagnosed with ADHD and healthy controls as well as whether there was a correlation between the plasma BDNF levels and both severity of ADHD symptoms and also cognitive functions.

RATIONALE

It is known that the worldwide prevalence of ADHD is approximately 5.3% in children and adolescents. ADHD may affect all aspects of a child's life; it affects not only the child but also the family as a whole. It is a chronic disorder which may impact upon many aspects of child's life including academic difficulties and social skills problems. To date biological markers are lacking. It has been suggested that BDNF may play a major in the etiopathogenesis of ADHD and in cognitive impairment that may co – exist, this association has not been sufficiently studied among Egyptian children.

HYPOTHESIS

BDNF level is decreased in children with ADHD in comparison to same aged normal children suggesting that BDNF plays a role in the etiopathogenesis of ADHD and affecting cognitive functions as well.

AIM OF THE WORK

The aim of the study is to:

1. Assess the relationship between BDNF level and diagnosis of ADHD.
2. Assess the relationship between BDNF level and symptoms of ADHD.
3. Assess the relationship between BDNF level and severity of symptoms of ADHD as assessed y Conner's parent's scale.
4. Assess the relationship between BDNF level and cognitive functions.

Chapter (1)

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention deficit hyperactivity disorder is a neurobehavioral developmental disorder ***(Faraone et al., 2003)*** mostly diagnosed in children with appearance of the first symptoms before the age of seven years old ***(Greenhil et al., 1998)***. It is characterized by pervasive and impairing symptoms of inattention, hyperactivity and impulsivity according to DSM-5 ***(American Psychiatric Association, 2013).***

World Health Organization (WHO) uses a different name —hyperkinetic disorder (HD)—but lists similar operational criteria for the disorder ***(World Health Organization, 1993)***.

ADHD is associated with a wide range of negative outcomes. It is a chronic disorder that may affect all aspects of a child's life including academic difficulties and social skills problems. It also causes a financial burden on families and society, which makes it a major public health problem ***(Polanczyk et al., 2007).***

Epidemiology of ADHD:

ADHD is the most common psychiatric disorder of childhood. Epidemiological studies indicate that ADHD is a prevalent disorder affecting from 6.7 to 7.8% of children worldwide ***(Thomas et al., 2015)***. This prevalence is higher in

Arabian countries reaching 9.4% in Egypt ***(Bishry et al., 2014)*** and 11.6% in Saudi Arabia ***(Homidi et al., 2013)***.

These reported differences in prevalence across countries might be related to differences in diagnostic criteria used, but also might be related to biological, cultural, and family factors ***(Bener et al., 2008).***

Male to female ratio is around 3:1 in children and adolescents, but it is believed that females are under diagnosed. ***(Wittchen et al., 2011)***

Etiology of ADHD:

The specific causes of ADHD are not known. The etiology of ADHD involves the interplay of a number of multiple genetic and environmental factors that may contribute to, or exacerbate ADHD ***(Bailly and Lionel, 2005).***

I) Biological Factors

A) Genetic Factors:

There is robust evidence from studies of a strong inherited contribution to ADHD. This finding is supported by twin studies, adoption studies, family studies and molecular genetics studies. It's heritability has been reported in some studies to be as high as 76% ***(Faraone et al., 2005)*** making it one of the highest among psychiatric disorders.

1- Family and adoption studies:

Family studies show that the occurrence of ADHD is high among the relatives of people with ADHD; it is 4-5 fold increase in risk with the first degree relatives compared to the general population. Second-degree relatives (such as cousins) are at increased risk for the disorder but their risk is lower than that seen in first-degree relatives. Adoption studies shows that ADHD rates are found to be greater in biological relatives of ADHD children than in the adoptive families ***(Sprich et al., 2000).***

2) Twin studies:

Generally, genetically based disorders should be very similar in twins and more similar in monozygotic (MZ) (identical) than in dizygotic (DZ) (fraternal) twins. Recently, there have been a number of twin studies that have looked at the concordance of ADHD in twins.

In general, twin studies indicate that the disorder is highly heritable and that genetics are a factor in about 75 percent of all cases ***(Burt, 2009)***.

Siblings of children with ADHD are more likely to develop the disorder than siblings of children without the disorder three to four times ***(Nolen- Hoeksema, 2013).***

3) Molecular genetic studies:

Despite substantial evidence for a genetic origin of ADHD, discoveries of specific genes or sets of genes causally linked to the disorder have yet to be made. Hypothesis-driven candidate gene approaches have linked ADHD to several genes, but inconsistent results and small effect sizes limit their interpretation. A meta-analysis found significant association of a handful of candidate genes with ADHD, but reported small odds ratios ranging from 1.15 to 1.54 and considerable variability in the reported associations. ***Hawi and colleagues (2002)*** highlighted ten candidate genes for which supportive evidence exists, such as meta-analyses, genome-wide association studies (GWAS), large-scale linkage studies, or animal model research. Many of the described gene products are involved in neurotransmission, with one half playing an important part in monoaminergic function (dopamine and serotonin transporters, and D4, D5, and 5-HT1B receptors). Other corroborated risk loci were mapped to genes involved in different aspects of synaptic transmission (SNAP25, NOS1, LPHN3, and GIT1). Table 1 shows hypothesized implications of these genes on behaviors related to ADHD. Other genes associated with ADHD include SERT, HTR1B, GRIN2A, ADRA2A, TPH2, and BDNF ***(Gizer et al., 2009, Kebir et al., 2009).*** Although these individual associations remain tentative and probably contribute only minimally to overall ADHD risk, they might nonetheless guide future investigation towards intermediate phenotypes ***(Gallo and Posner, 2016).***

Table (1): Selected candidate genes implicated in attention-deficit hyperactivity disorder (ADHD).

	Gene product or function	Hypothesised links to ADHD-related phenotypes
SLC6A3 (DAT)	Dopamine re-uptake, transporter	Inhibition, attentional flexibility, inattention, impulsivity
DRD4	Dopamine D4 receptor	Verbal memory skills, Inattention Hyperactivity
DRD5	Dopamine D5 receptor	Inattention, Response time variability
SLC6A4 (SERT)	Serotonin reuptake, transporter	Delay aversion Motivational dysfunction
HTR1B (5HT1B)	Serotonin receptor	Inattention, response inhibition
SNAP25	Neurotransmission	Impulsivity, Inattention
NOS1	Nitric oxide synthase, neurotransmission, neuroplasticity	Impulsivity, Aggressivity, Hyperactivity
SLC9A9	Ion transport	Impulsivity
LPHN3	GPCR, cell adhesion, signal transduction	Inattention
GIT1	GPCR kinase, vesicle trafficking, cell adhesion, cell migration	Learning deficits
CDH13	Cell-cell adhesion and neural cell growth	Working memory deficits, Hyperactivity and impulsivity
GFOD1	Glucose-fructose oxidoreductase-domain containing 1, electron transport	Not described
CNR1	Cannabinoid receptor, neurotransmission	Impulsivity, Drug abuse
CHRNA7	Nicotinic acetylcholine receptor 7	Inattention

B) Brain structure

Individuals with ADHD have a smaller brain volume by about 3-8 % which could explain some of the cognitive and behavioral symptoms of ADHD ***(Kieling et al., 2008; Biederman, 2005)***.

A variety of brain subregions including frontal and parietal cortexes, basal ganglia, cerebellum, hippocampus, and

corpus callosum were found to be involved in ADHD ***(Giedd et al., 2010)***.

These longitudinal studies have shown a developmental delay of cortical thickness in ADHD, with greatest differences between ADHD and controls in maturation of the middle prefrontal cortex. Interestingly, normalization of volumes in different brain regions such as the parietal cortex and the hippocampus parallel clinical improvement of symptoms, whereas progressive volume loss of cerebellar regions and hippocampus were associated with persistent symptoms ***(Giedd et al., 2010).***

C) Neurotransmitter pathways:

Researchers believe that ADHD is associated with functional impairment in some neurotransmitters especially dopamine and norepinephrine. There may be also abnormalities in serotoninergic and cholinergic pathways ***(Castellanos and Proal, 2012; Cortese, 2012).***

Abnormalities in dopamine metabolism have long been implicated in the etiology of ADHD for many reasons ***(Kirley et al., 2003)*** for example, Studies demonstrated that lesions of the dopaminergic neurons of the ventral tegmental area resulted in hyperactivity, hyper-responsivity, poor response to stress, and a spectrum of other disorders ***(Moal and Simon, 1991).***

Studies have shown that chemical destruction of frontal lobe dopaminergic neurons shortly after birth produced an animal model of ADHD that responded to stimulants ***(Shaywitz et al., 1976).*** It was reported that there is low CSF homovanillic acid in children with ADHD, while more recent studies have shown a positive correlation between CSF homovanillic acid and scores of hyperactivity and conduct disorder ADHD ***(Gerra et al., 2007).***

Also, Brain imaging studies showed defects in the dopamine-rich striatum in ADHD ***(Krause et al., 2003)***.

Further evidence has demonstrated the effectiveness of dopaminergic agonists in the treatment of ADHD ***(La Fougere et al., 2006).***

D) Pathophysiology

The dopamine and norepinephrine pathways play a role in the pathophysiology of ADHD. These pathways project to the prefrontal cortex and striatum and are responsible for modulating executive functions (EF), motivation and reward perception ***(Cortese, 2012).***

ADHD involves problems with executive functions which are a group of mental processes that are essential to regulate, control, and manage daily life tasks. The criteria for an executive function deficit are met in 30–50% of children and adolescents with ADHD ***(Lambek et al., 2010).***

Some of these impairments include problems with organization, time keeping, excessive procrastination, concentration, processing speed, regulating emotions, and utilizing working memory ***(Brown, 2008).***

The exact pathophysiology of Attention Deficit Hyperactivity Disorder (ADHD) is not clear. The underlying brain regions predominantly thought to be involved are frontal and prefrontal; the parietal lobe and cerebellum may also be involved. Research on children with ADHD has shown a general reduction of brain volume, but with a proportionally greater reduction in the volume of the left-sided prefrontal cortex. These findings suggest that the core ADHD features of inattention, hyperactivity, and impulsivity may reflect frontal lobe dysfunction ***(Krain and Castellanos, 2006).***

Neuroimaging studies in ADHD have not always given consistent results and are used only for research and not diagnostic purposes ***(Merck, 2010).***

A PET scan study by Alan et al. found that global cerebral glucose metabolism was 8 percent lower in medication-naive adults who had been hyperactive since childhood ***(Zametken et al., 1990)***.

In contrast, the motor cortex in the ADHD patients was seen to mature faster than normal, suggesting that both slower development of behavioral control and advanced motor